FUNCTIONAL NEUROIMAGING STUDIES OF DEPRESSION: The Anatomy of Melancholia

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KEY WORDS: PET (positron emission tomography), cerebral glucose metabolism, cerebral blood flow, MRI (magnetic resonance imaging), major depression

ABSTRACT

Functional brain imaging techniques, which permit noninvasive measures of neurophysiology and neureceptor binding, are powerful and sensitive tools for research aimed at elucidating the pathophysiology of major depression. The application of these technologies in depression research has produced several studies of resting cerebral blood flow (BF) and glucose metabolism in subjects imaged during various phases of illness and treatment. This review examines these data and the principles relevant to their interpretation and discusses the insights they provide into the anatomical correlates of depression. Within the anatomical networks implicated in emotional processing by other types of evidence, these BF and metabolic data demonstrate that major depression is associated with reversible, mood state–dependent, neurophysiological abnormalities in some structures and irreversible, trait-like abnormalities in other structures. In some of the regions in which trait-like abnormalities appear, abnormal metabolic activity appears at least partly related to the anatomical abnormalities identified in magnetic resonance imaging (MRI) studies of depression.

APPLICATION OF NEUROIMAGING IN DEPRESSION RESEARCH

The major depressive disorders appear particularly tractable to functional imaging approaches aimed at elucidating their pathophysiology because they
have been associated with disruptions of brain function in the absence of gross neuropathology (1). Their episodic nature and responsiveness to treatment permit imaging in both symptomatic and asymptomatic states. The similarity between some depressive symptoms and emotional states that can be expressed by nondepressed subjects permits comparisons of the hemodynamic changes associated with the depressed state with those occurring in healthy subjects during experimentally induced sadness or anxiety (2). The insights provided by functional neuroimaging studies of depression may ultimately localize specific brain regions for histopathological assessment, elucidate antidepressant treatment mechanisms, and guide pathophysiology-based classification of depression.

The clinical capabilities of these tools for determining diagnoses or guiding treatment decisions have not been established (3). The abnormalities identified in BF and metabolic imaging studies of depression have consisted of differences in mean tracer-uptake values between groups of depressives and controls. The sensitivity for detecting abnormalities in individual cases has been limited by the small magnitude of such differences relative to the variability of imaging measures. None of these abnormalities has been shown to sensitively and specifically distinguish individual depressives from healthy subjects and from subjects who have other illnesses.

SIGNIFICANCE OF REGIONAL BLOOD FLOW AND GLUCOSE METABOLISM

Changes in local BF and glucose metabolism during mental activity predominantly reflect net differences in the summed metabolic activity associated with terminal field synaptic transmission (4, 5). Dynamic brain imaging can thus be used to provide maps of regional neural function (4). However, these measures are also affected by cerebrovascular disease, thyroid dysfunction, gray-matter reductions associated with atrophy or hypoplasia, and other abnormalities that exist in some depressive subgroups (6, 7). Regional BF or metabolic differences between depressives and controls may thus reflect either the physiological correlates of depressive emotions and thoughts or pathophysiological changes that predispose subjects to or result from affective disease.

The physiological correlates of depressive symptoms presumably appear as reversible changes in local BF and metabolism that normalize after effective treatment. These changes can to some extent be reproduced in healthy subjects imaged while performing tasks that mimic the corresponding depressive manifestation. For example, in primary major depressive disorder (MDD), the medial orbital cortex shows abnormally elevated BF and metabolism in the depressed phase relative to the remitted phase (Figure 1a, see color section, p. C-
8). Medial orbital BF also increases during experimentally induced states of anxiety or sadness in healthy subjects (2, 8, 9, 10).

In contrast, BF and metabolic abnormalities in depression may also reflect pathophysiological changes in synaptic transmission associated with altered neurotransmitter synthesis or receptor sensitivity, or with alterations in the number of synaptic connections resulting from regional atrophy or hypoplasia. Such abnormalities may be evident regardless of whether subjects are exhibiting symptoms of depression (14, 15).

TECHNICAL ISSUES RELEVANT TO THE INTERPRETATION OF IMAGE DATA

Consensus regarding the functional anatomical correlates of depression has been difficult to achieve because the conclusions disagree across studies. However, many of the conflicts within the literature can be resolved by considering technical issues related to subject selection, image acquisition, and image analysis (3).

Subject Selection

Most functional imaging studies of depression involve relatively small sample sizes. This design limitation coupled with the subtle magnitude of the BF and metabolic differences between depressives and controls relative to the variability of such measures reduces the sensitivity of studies for detecting intergroup differences and for replicating findings across studies. Consequently, subject selection criteria that reduce the variability of imaging measures are often required to improve statistical sensitivity.

Medication effects are an important source of variability in functional imaging studies. Regional BF and metabolism in some prefrontal cortical and limbic areas of interest in depression are reduced by antidepressant, antipsychotic, and antianxiety drugs (3, 16, 17). Blood flow or metabolic image data acquired from depressives medicated with these drugs are thus difficult to interpret without the availability of unmedicated baseline scans for comparison. Nevertheless, most published studies of depression report image data confounded by such medication effects, potentially introducing artifactual differences or obscuring true biological differences between depressives and controls.

Another source of variability is introduced by the clinical heterogeneity inherent within the depressive syndrome, as diverse signs and symptoms may have distinct neurophysiological correlates (1). For example, a depressed patient exhibiting prominent anxiety, obsessive ruminations, insomnia, and psy-
chomotor agitation may show dissimilar imaging findings from one who pre-
dominantly manifests apathy, inactivity, excessive sleep, and psychomotor
slowing. Nevertheless, few studies have had sufficiently large subsamples of
depressives manifesting clinical factors to sort out the relative contributions of
each factor to the variability of imaging measures.

A related concern for imaging studies of depression is that the major de-
pressive syndrome is heterogenous with regard to etiology and pathology (1).
Biological heterogeneity is evidenced by the variety of antecedents to depres-
sive syndromes; the diversity of responses to somatic or psychological thera-
pies; and the variable presence of neuroendocrine, neurochemical, and cir-
cadian rhythm disturbances in depressive samples (1). If depression is associ-
ated with multiple pathophysiological states, it can presumably be character-
ized by an assortment of distinct functional imaging abnormalities. The litera-
ture confirms this hypothesis, since some subtyping of depressed subjects ap-
pears critical for reducing the variability of image data. Examples discussed
below include the distinction between primary and secondary depressive dis-
orders and between elderly depressives with a late versus an early age-of-
ilness-onset.

**Implications of Structural Abnormalities for Functional
Neuroimaging**

Presumably related to this biological diversity, some subsets of depressed sub-
jects have neuromorphological abnormalities based on structural MRI or CT
imaging studies (3). Depressives who are bipolar, psychotic, or elderly (with a
late age-of-depression-onset) have an elevated incidence of ventricular and
sulcal enlargement and have reductions in some lobar or gyral volumes (3).
The tissue reductions reflected by such structural imaging abnormalities de-
crease the magnitude of imaging measures from positron emission tomogra-
phy (PET) and single photon emission tomography (SPET) images because of
the low spatial resolution of these images (6). Where atrophy or hypoplasia ex-
ists, the tracer uptake measured within the corresponding PET or SPET image
voxel (volume element) reflects lower proportions of gray and white matter
relative to the proportion of cerebrospinal fluid (CSF). The measured BF or
metabolism is thus reduced via partial volume averaging effects of emphasizing
CSF, which is metabolically inactive (6).

As a result, findings of decreased BF and metabolism in depressives who
exhibit such abnormalities are difficult to interpret. Since the incidence of ven-
tricular and sulcal enlargement does not appear increased in nondelusional,
unipolar depressives who developed the disorder at a young age, the image
data from this group must constitute the benchmark against which physiologi-
cal imaging measures in other depressive subtypes are compared (1, 3). Neverth-
least, some focal areas of reduced gray matter volume appear to exist even in young, nondelusional, familial unipolar depressives. Such findings empha-
size the importance of evaluating areas in which BF and metabolism are irre-
versibly decreased in depressives relative to controls using MRI-based mor-
phometric and postmortem histopathological studies (14; see also Figure 2, p. C-10).

Another type of structural abnormality that typically shows up in MRI im-
ages from elderly depressives who have a late age-of-depression-onset in-
volves white matter hyperintensities (WMH) and lacunar infarctions (18).
Postmortem evidence indicates that these hyperintensities reflect arterioscle-
rotic or ischemic disease (18–20). As expected, imaging studies demonstrate
that elderly depressives who have WMH have decreased BF and metabolism
in the involved areas relative to age-matched depressives who do not have
WMH (21). In the presence of cerebrovascular disease, the findings of reduced
BF and metabolism cannot be interpreted as providing information related to
local synaptic transmission. Nevertheless, most functional imaging studies of
depression in the elderly have not excluded (or even identified) subjects who
show MRI evidence of cerebrovascular disease.

Image Acquisition and Analysis Issues

Functional imaging studies of depression have been performed using PET,
SPET, and nontomographic multidetector systems, which each present their
own set of unique technical considerations (3, 4). The precision and resolution
of localizing functional imaging measures has been enhanced by progressive
improvements in spatial resolution [to 4 mm for the newest PET cameras and
0.5 mm for functional MRI (fMRI)], techniques for co-registering PET and
MRI images, and statistical mapping methods that delimit inherent physiologi-
cal differences between depressives and controls (3; see also Figures 1a–c and
2, pp. C-8, C-9, C-10). Localization is now limited as much by the anatomical
variability across individuals as by the spatial resolution of imaging technolo-
gies. Nevertheless, most published studies were performed using techniques
that more severely constrain the size and the location of brain structures from
which measures can be obtained (3, 4). For example, images acquired using
SPET or nontomographic multidetector systems and inhalation of $^{133}$Xe pro-
vide BF measures limited to the cortical gray matter lying near the scalp (4).
Moreover, although PET affords relatively high spatial resolution and sensi-
tivity for deep structures, in most PET studies, the images have been blurred
(by filtering) to spatial resolutions of 2 cm or more prior to analysis. This prac-
tice reduces the effects of anatomical variability across subjects, but it also sac-
ifices the method's ability for resolving small structures. Such considerations
thus influence the size of regions that can be resolved in functional imaging studies, the boundaries for defining regions of interest, and the sensitivity for replicating results across studies.

Another technical issue applied variably across imaging studies involves the normalization of regional measures by dividing by global or hemispheric measures (4). Because of the small subject sample sizes involved in imaging studies, normalization is usually required to reduce the variability of regional values so that intergroup differences can be detected. Whole-brain BF and glucose metabolism have not significantly differed between depressed and control samples in most studies of unmedicated, mid-life depressives (e.g. 14, 16, 22). In contrast, global BF and metabolism correlated inversely with thyroid stimulating hormone (TSH) levels and were decreased in a depressed sample whose mean TSH value exceeded that of the control sample (7). Since modest elevations of TSH are common in major depression, these data suggest that absolute BF and metabolic measures in depressive samples may be difficult to interpret unless covaried for TSH levels. This problem further emphasizes the benefits of normalizing regional values to exclude global effects, which would minimize the global impact of differences in mean TSH levels between depressed and controls on regional BF and metabolic values (7).

ABNORMALITIES OF CEREBRAL BLOOD FLOW AND METABOLISM IN DEPRESSION

Studies comparing depressed patients to healthy controls have identified BF and metabolic differences between groups in multiple regions, consistent with the expectation that the emotional, cognitive, psychomotor, neurovegetative, neuroendocrine, and neurochemical disturbances associated with depression implicate extended anatomical networks involving numerous brain structures. This review highlights the major findings delineated by well-designed studies and replicated across neuroimaging laboratories. The results of studies that are confounded by medication effects (which occupy a large proportion of the literature) are not included.

Prefrontal Cortical Abnormalities in Mood Disorders

The prefrontal cortex (PFC) represents 40–50% of the volume of the human brain. Numerous anatomical and functional subdivisions of the PFC have been based on anatomical connectivity, cytoarchitectonic distinctions, electrophysiological studies, lesion analyses, and PET/fMRI brain mapping studies (12, 24). Within the PFC, performance of either cognitive or emotional processing tasks generally results in BF increases in multiple, distinct areas (in patterns specific to the mental operations demanded by each type of task) and in
focal BF decreases in additional prefrontal areas (4, 25, 26). The latter putatively reflect regions that are deactivated to facilitate task performance via suppression of unattended, potentially competing background processes (2, 27). The complex activation/deactivation patterns formed by these increases and decreases in physiological activity are interpreted within the context of data from other brain mapping and lesion-analysis studies.

Many studies of the dorsolateral and the dorsomedial PFC found that BF and metabolism are decreased in depressives relative to controls (Table 1). These abnormalities have been reversible with effective antidepressant therapy in some studies (28, 29; but see 30, 31).

Another prefrontal area in which BF and metabolism are decreased in unipolar and bipolar depressives is in the anterior cingulate gyrus ventral to the genu of the corpus callosum (14; see also Figure 2). This decrement appears to be at least partly explained by a corresponding reduction in cortex, as MRI-based neuromorphometric measures demonstrate an abnormal reduction in the mean gray matter volume of the left subgenual PFC in familial bipolar and unipolar depressed samples (6, 14). Consistent with the hypothesis that an anatomical abnormality partly accounts for the metabolic reduction in the subgenual PFC, metabolism in this region does not normalize following treatment (14).

Neurophysiological activity generally increases abnormally in the ventrolateral, lateral orbital, and posteromedial orbital portions of the PFC (Figure 1a,b, p. C-8) and in the portion of the anterior cingulate gyrus anterior to the genu of the corpus callosum (i.e. the pregenual anterior cingulate) in unmedicated, primary, unipolar depressives (Table 1). When depressives are imaged both before and during effective antidepressant treatment, ventrolateral prefrontal and orbital cortex activity decrease in the remitted phase relative to the depressed phase (Table 2). In contrast, the effects of treatment upon activity in the pregenual anterior cingulate have been more variable: Two SPET studies have reported that anterior cingulate BF increases rather than decreases following treatment (29, 46; see Table 2).

**Abnormalities in Related Subcortical and Limbic Structures**

The ventrolateral, ventromedial (i.e. anterior cingulate), and orbital areas of the PFC where BF and metabolism are abnormal in the depressed phase of MDD all share extensive interconnections with the amygdala, the mediodorsal nucleus of the thalamus, and the ventral striatum (the ventromedial caudate and the nucleus accumbens), structures consistently implicated by other types of evidence in emotional behavior (12, 50). In the left (and possibly the right) amygdala and the medial thalamus, BF and metabolism are abnormally increased in unipolar and bipolar depression (37, 38, 41, 42, 51, 52; see also Fig-
<table>
<thead>
<tr>
<th>References</th>
<th>Sample Size</th>
<th>Imaging Technique</th>
<th>Blood flow or glucose metabolism in DEP relative to CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxter et al (32)</td>
<td>14/14</td>
<td>PET, $^{18}$FDG</td>
<td>↑ medial orbital (BL)$^b$</td>
</tr>
<tr>
<td>Baxter et al (28)</td>
<td>10/12</td>
<td>PET, $^{18}$FDG</td>
<td>N/A</td>
</tr>
<tr>
<td>Bench et al (33)</td>
<td>33/23</td>
<td>PET, H$_2^{15}$O</td>
<td>N/A</td>
</tr>
<tr>
<td>Biver et al (34)</td>
<td>12/12</td>
<td>PET, $^{18}$FDG</td>
<td>↑ medial and lateral orbital (BL)</td>
</tr>
<tr>
<td>Buchsbaum et al (35)</td>
<td>4/24</td>
<td>PET, $^{18}$FDG</td>
<td>↑ frontal/occipital ratio (↑ ventral frontal metabolism shown in ANOVA image)</td>
</tr>
<tr>
<td>Cohen et al (36)</td>
<td>7/38</td>
<td>PET, $^{18}$FDG</td>
<td>↑ medial orbital</td>
</tr>
<tr>
<td>Drevets et al (37)</td>
<td>13/33</td>
<td>PET, H$_2^{15}$O</td>
<td>↑ ventrolateral, lateral orbital (L), ↑ pregemual ant. cingulate</td>
</tr>
<tr>
<td>Drevets et al (38)</td>
<td>31/17</td>
<td>PET, $^{18}$FDG</td>
<td>↑ lateral &amp; medial orbital (BL)$^f$, ↓ subgenual ant. cingulate$^f$</td>
</tr>
<tr>
<td>Ebert et al (39)</td>
<td>10/8</td>
<td>SPET, $^{99m}$TcHMPAO</td>
<td>↑ orbital (BL)$^e$</td>
</tr>
<tr>
<td>Maes et al (17)</td>
<td>30/12</td>
<td>SPET, $^{99m}$TcHMPAO</td>
<td>N/A</td>
</tr>
<tr>
<td>Mayberg et al (40)</td>
<td>18/15</td>
<td>PET, $^{18}$FDG</td>
<td>↑ pregemual ant. cingulate in treatment responders, but ↓ in nonresponders; NS orbital$^i$</td>
</tr>
<tr>
<td>Mentis et al (41)</td>
<td>11/12</td>
<td>PET, $^{18}$FDG</td>
<td>↑ orbital and lateral prefrontal</td>
</tr>
<tr>
<td>Nofzinger et al (42)</td>
<td>6/10</td>
<td>PET, $^{18}$FDG</td>
<td>↑ medial orbital (L) ↑ lateral orbital (R)</td>
</tr>
<tr>
<td>Silverskiöld &amp; Risberg (16)</td>
<td>31/31</td>
<td>Multidetector probes, $^{133}$Xe$^j$</td>
<td>NS (trend toward ↑ left ventrolateral)</td>
</tr>
<tr>
<td>Trivedi et al (43)</td>
<td>24/24</td>
<td>SPET, $^{99m}$TcHMPAO</td>
<td>↑ inferior frontal g. (R)</td>
</tr>
<tr>
<td>Uytendhoef et al (44)</td>
<td>16/20</td>
<td>Multidetector probes, $^{133}$Xe$^j$</td>
<td>↑ left “frontal ratio” (which included ventrolateral)</td>
</tr>
<tr>
<td>Wu et al (45)</td>
<td>15/15</td>
<td>PET, $^{18}$FDG</td>
<td>↑ ant. cingulate$^e$, orbital N/A</td>
</tr>
</tbody>
</table>
NEUROIMAGING STUDIES OF DEPRESSION

Abbreviations: DEP, depressed subjects; CON, control subjects; $^{18}$FDG, $^{18}$F-fluorodeoxyglucose is used to measure glucose metabolism; $^{15}$O (oxygen-15 water), $^{99m}$Tc-HMPAO (technetium-99 HMPAO), and $^{133}$Xe (xenon-133) are used to measure blood flow; ant, anterior; g, gyrus; Bl, bilateral; L, left; R, right; NS, difference assessed and not significant; N/A, region not assessed. ↑ and ↓ indicate increases and decreases, respectively, in the depressives relative to the controls. Image data from studies which are uninterpretable due to confounding medication effects are not reviewed unless data were separately assessed for the unmedicated subsample. Data from studies of "secondary" depression and bipolar depression are addressed separately (see text and Table 3). Some of these studies included bipolar subjects in their depressed samples, but only the results from the unipolar subsample are reported here (unless data were not presented separately for bipolar and unipolar subjects). The descriptive terms used to locate regions vary across study, and in some cases distinct terms may be used to describe the same area. Conversely, studies using the same term may be describing different cortical areas (e.g., the "dorsolateral prefrontal cortex" spans several cm$^2$ and encompasses numerous resolution elements) since most studies have not used localization techniques that employ a standardized coordinate system or MRI-based landmarks.

This paper compared regional metabolism between subjects with obsessive-compulsive disorder and subjects who were either primary unipolar depressives or healthy controls. While the difference between depressives and controls was not statistically assessed in this paper, the published values for the orbital-to-hemisphere ratio in the depressives (N=14; right: 1.17±0.06, left: 1.14±0.05) and the controls (N=13; right 1.11±0.08, left: 1.09±0.06) showed differences which were similar in magnitude and variability to the differences found in other studies using images of similar resolution, and would be significant by t-test (right: P<0.05, left: P<0.02) [from Table 3 of Baxter et al (27)].

Nineteen of the depressives were imaged while receiving various medications. The reported abnormalities were initially identified using image data from the entire depressed sample (N=33), but the difference between DEP and CON was also confirmed in the unmedicated subsample (N=14) post hoc.

This study identified abnormalities using a statistical image that excluded pixels in the orbital cortex, because the images acquired did not extend into this ventral structure for all subjects (Dolan, personal communication).

Subjects also met criteria for winter seasonal affective disorder.

Abnormalities significant in subgroup meeting criteria for familial pure depressive disease, but not for subgroup with familial loading for alcoholism.

Abnormality found only in subgroup who proved responsive to sleep deprivation.

Reflects the sample size for the unmedicated subjects only, who were independently compared to controls and to another 13 benzodiazepine-treated subjects.

Five of these subjects had been subchronically treated with antidepressant drugs prior to scanning. It is unclear whether subchronic antidepressant drug therapy has the same effect of decreasing orbital metabolism as does chronic treatment (Table 2).

Blood flow is only measured near the scalp using this technique, so no results are available for the orbital or the cingulate cortices (see text).
In contrast, in unipolar—but not bipolar—depressives, BF and metabolism are reduced abnormally in the caudate (37, 22, 53).

Abnormalities in Other Brain Areas

Regional BF and metabolic abnormalities in other brain areas have been replicated less consistently. In areas of the lateral temporal and the parietal cortex, some studies have found reduced regional BF and metabolism (37, 34, 36, 54). Some of these areas appear to be involved in processing sensory information. The significance of BF reductions in such areas in depression is unclear. These abnormalities may reflect areas that become deactivated as the brain engages in emotional processing, and they may relate to some of the neuropsychological impairments seen in depression (2).

Table 2  Antidepressant treatment effects upon ventral prefrontal cortical blood flow and metabolism in major depression

<table>
<thead>
<tr>
<th>References</th>
<th>Treatment modality</th>
<th>Change in BF or glucose metabolism post- vs pretreatment scans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonne et al (29)</td>
<td>ECT</td>
<td>↑ anterior cingulate in responders, NS in ventral anterolateral PFC</td>
</tr>
<tr>
<td>Cohen et al (36)</td>
<td>phototherapy</td>
<td>↓ left ventrolateral PFC</td>
</tr>
<tr>
<td>Drevets &amp; Raichle (47)</td>
<td>desipramine</td>
<td>↓ ventrolateral PFC and orbital C</td>
</tr>
<tr>
<td>Drevets et al (48)</td>
<td>sertraline</td>
<td>↓ orbital C in responders</td>
</tr>
<tr>
<td>Ebert et al (39)</td>
<td>sleep deprivation</td>
<td>↓ orbital C in responders</td>
</tr>
<tr>
<td>George et al (49)</td>
<td>RTMS</td>
<td>↓ orbital C in responders</td>
</tr>
<tr>
<td>Goodwin et al (46)</td>
<td>various drug treatments</td>
<td>↑ anterior cingulate, NS in ventral anterolateral</td>
</tr>
<tr>
<td>Nobler et al (30)</td>
<td>ECT</td>
<td>↓ left ventrolateral PFC, responders</td>
</tr>
<tr>
<td>Rubin et al (31)</td>
<td>nortriptyline or sertraline</td>
<td>↓ left ventrolateral PFC, responders</td>
</tr>
<tr>
<td>Trivedi et al (43)</td>
<td>fluoxetine</td>
<td>↓ left orbital C</td>
</tr>
<tr>
<td>Wu et al (45)</td>
<td>sleep deprivation</td>
<td>↓ anterior cingulate, responders</td>
</tr>
</tbody>
</table>

a Abbreviations: C, cortex; ECT, electroconvulsive therapy; PFC, prefrontal cortex; RTMS, repeated transcranial magnetic stimulation. ↑, ↓, and NS indicate increases, decreases, or no significant changes, respectively, in the treated relative to the untreated state for regions assessed. Not all studies examined the same regions, and the absence of a listed result for a specific region indicates that no image data were provided for that region. The changes in these ventral PFC regions show similar results to studies of antidepressant drug treatment in obsessive compulsive disordered samples (3). In contrast to these ventral prefrontal changes in depression, BF and metabolism in the dorsal anterior cingulate and the dorsolateral PFC have been shown to increase in some studies of depression (e.g. 28, 40), but to decrease in others (41, 42) following effective antidepressant treatment.

b The treatment-associated change reported in this study was not shown by paired statistical tests but rather by the observation that in the treatment responders, the abnormal increase that was evident pretreatment was not present post-treatment.

c These studies were performed using the radiotracer, xenon-133, which only provides BF measures near the scalp. Thus results were not available for the orbital or the cingulate cortices (see text).
Finally, abnormally increased BF has been reported in the cerebellar vermis in major depression (33). As in the case of the orbital cortex, BF in the vermis increases in experimentally induced states of anxiety or sadness in healthy subjects and in anxiety states elicited in subjects who have anxiety disorders (8, 55, 68). This finding affects the interpretation of the results of early SPET studies of depression, which normalized flow in all other brain regions by cerebellar flow. For example, Philpot et al (54) showed that while comparisons of regional-to-cerebellar ratios resulted in apparent flow reductions in most regions assessed in depressives relative to controls, when the same data were recalculated as ratios relative to the ipsilateral occipital cortex (where flow generally does not differ between depressives and controls), only the right parietal cortex BF ratio remained significantly decreased in depression.

**Primary Major Depressive Subtypes Requiring Special Considerations**

The abnormal BF and metabolic increases in the ventral PFC and the amygdala have not been demonstrable in all primary depressive samples. Elderly depressives who have WMH have not demonstrated abnormal elevations in these areas (e.g. 21). In addition, depressive subgroups who are nonresponsive to antidepressant treatments have shown either reductions (40) or no differences (39, 45) in anterior cingulate and orbital cortex activity with respect to control groups.

Elderly depressives with MRI evidence of cerebrovascular disease (seen as WMH or lacunae in T2 weighted images) show reduced BF and metabolic measures, putatively on a vascular/ischemic basis (18, 21). To examine the physiological correlates of depression in elderly samples, it is thus necessary either to exclude such subjects (who are clinically characterized by having an age-of-depression-onset after age 60 and relatively greater degrees of cognitive impairment) or to study such subjects as their own controls in pre- versus posttreatment comparisons. A study of elderly depressives that excluded subjects who had moderate or severe WMH reported the same findings as found in young depressives, namely, increased BF in the orbital cortex, the ventrolateral PFC, and the amygdala (41). In a study of elderly depressed samples that included subjects who had WMH, successful treatment with either electroconvulsive therapy (ECT) or antidepressant drug therapy resulted in a further decrease in BF in the left ventrolateral PFC (30, 31). These data converge with those presented in Table 2 to indicate that the depressed state is associated with elevated ventral prefrontal activity relative to the remitted state.

Imaging studies in bipolar depressives also appear to be confounded by neuromorphological abnormalities, as volumetric reductions in some prefron-
tal cortical and limbic structures have been reported in bipolar samples (14, 56). Such morphometric abnormalities presumably reduce the magnitude of PET and SPET measures in the vicinity of these structures (6). Consistent with this concern, identification of hypermetabolism in the orbital cortex, the amygdala, and the medial thalamus in bipolar depressives has in some studies depended on the use of high (e.g. 5-mm full-width at half-width maximum [FWHM; see Reference 4 for description]) rather than low spatial resolution PET images (e.g. 17-mm FWHM), since the effects of partial volume averaging diminish as resolution increases (51).

Finally, some means of enriching subject samples for depressives likely to have biological markers for depression may be needed to demonstrate evidence of functional neuroimaging abnormalities in small samples. For example, unipolar depressives with familial loading for alcoholism are also less likely to have neuroendocrine and sleep EEG abnormalities (i.e. other biological markers for depression) as compared to familial pure depressives (1). Similarly, samples of unipolar depressives with familial loading for alcoholism have mean metabolic values in the above-mentioned regions, between those of healthy controls and of unipolar depressives with familial-pure depressive disease (38). In other studies, elevated anterior cingulate, orbital, and amygdala activity have been shown in subsets whose depressive symptoms improve with total sleep deprivation but not in subgroups who are unresponsive to sleep deprivation (39, 45).

**Anatomical Circuits Related to Depression**

Since alterations in BF and metabolism primarily reflect changes in local synaptic activity, interpreting the regional abnormalities in depression requires consideration of anatomical connectivity. Elevated regional BF and metabolism may signify increased neurotransmission (excitatory or inhibitory) from afferent projections arising from within the same structure or from a distal structure (4, 5). Conversely, reductions in regional BF or metabolism may reflect a decrease in afferent transmission (e.g. owing to active inhibition at upstream synapses).

The imaging data in primary major depression converge with evidence from lesion analyses to implicate circuits involving parts of the frontal and temporal lobes along with related parts of the striatum, pallidum, and thalamus in the pathophysiology of depression (1, 37, 12). For example, the findings in primary unipolar depressives of abnormally increased BF and metabolism in the ventrolateral and orbital portions of the PFC, the amygdala, and the medial thalamus (Figure 1a–c, pp. C-8, C-9), coupled with indications of reduced flow in the medial caudate, implicate two interconnected circuits in the patho-
physiology of depression. A limbic-thalamo-cortical circuit involves the amygdala, the mediodorsal nucleus of the thalamus (in the medial thalamus), and the ventral PFC; and a limbic-striatal-pallidal-thalamic circuit involves related parts of the striatum and the ventral pallidum as well as the components of the other circuit (37).

The amygdala and the prefrontal cortical regions are connected by excitatory projections with each other and with the mediodorsal nucleus of the thalamus. As a result, increased metabolic activity in these structures would presumably reflect increased synaptic transmission through the limbic-thalamo-cortical circuit. Consistent with this hypothesis, neurosurgical procedures that ameliorate treatment-resistant depression interrupt projections within these circuits, and effective antidepressant drug treatments reduce BF and metabolism in the amygdala, the ventral PFC, and the medial thalamus (37, 47, 48). However, transmission through these circuits likely differs across depressive subtypes, since the lesions involving the PFC (i.e. tumors or infarctions) and the diseases of the basal ganglia (e.g. Parkinson’s or Huntington’s diseases), which are associated with higher rates of depression than other similarly debilitating conditions, result in dysfunction at distinct points within these circuits that affect synaptic transmission in different ways (1). This concept finds an analogy in the more dorsal motor circuitry, in which lesions at various points can result in paraplegia but are associated with dissimilar patterns of abnormal synaptic transmission.

Functional Imaging Studies of Secondary Depression

Consistent with a circuitry-based approach to the functional anatomy of depression, results of imaging studies of depressive syndromes arising secondary to neurological disorders generally differ from those reported for primary depressive syndromes. In contrast to the findings of increased BF or metabolism in parts of the orbital cortex in primary depressives (Table 1), orbital BF or metabolism is reportedly decreased or not significantly different in subjects who have depressive syndromes arising secondary to Parkinson's disease, Huntington's disease, or basal ganglia infarction relative to nondepressed subjects who have the same illnesses (Table 3). Similarly, in the dorsolateral PFC, BF and metabolism are generally not significantly different between subjects who have neurological diseases who meet criteria for major depression and those who do not, which contrasts with the findings in primary depression (Table 1).

Studies of the physiological correlates of depressive symptoms in subjects who have primary psychiatric disorders other than mood disorders have reported abnormalities that more closely resemble those found in primary depressive samples. In a study of subjects who had bulimia nervosa (63), metabo-
Table 3 Regional blood flow and metabolic abnormalities in the ventral prefrontal cortex in primary versus secondary neuropsychiatric syndromes

<table>
<thead>
<tr>
<th></th>
<th>Primary</th>
<th>Secondary</th>
<th>References (and primary diagnoses)</th>
</tr>
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<tbody>
<tr>
<td>Unipolar major depression</td>
<td>↓</td>
<td>Mayberg et al (57) (Parkinson’s disease)c</td>
<td></td>
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<tr>
<td></td>
<td>↑ b NS</td>
<td>Mayberg et al (58) (Huntington’s disease)c</td>
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<tr>
<td></td>
<td></td>
<td>Mayberg et al (59) (basal ganglia infarction) f</td>
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<td></td>
<td></td>
<td>Ring et al (60) (Parkinson’s disease) f</td>
<td></td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>↓ d NS</td>
<td>LaPlane et al (61) (basal ganglia lesions) f</td>
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<tr>
<td></td>
<td></td>
<td>George et al (62) (Tourette’s syndrome)f</td>
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Abbreviations: D, disease; NS, difference not significant. Additional studies of subjects who had depressive symptoms but did not meet criteria for the major depressive syndrome are reviewed in the text.

BF and metabolism generally increased in unmedicated, primary depressives versus controls (Table 1).

Comparison between depressed and nondepressed subjects with the same illness.

BF and metabolism generally increased in unmedicated subjects with primary obsessive-compulsive disorder relative to controls (3, 32).

Subjects with secondary obsessive-compulsive syndrome compared to healthy controls.

Comparison between Tourette’s subjects who manifest obsessions and compulsions vs. Tourette’s subjects without such features.

lism trended toward being abnormally reduced in the dorsolateral PFC, where it correlated negatively with depression ratings [as reported in primary depression (28)]. Metabolism tended to be abnormally elevated in the orbital cortex, where it correlated negatively with obsessive-compulsive ratings. These results are similar to the relationships found between posterior orbital BF and obsession ratings in primary obsessive-compulsive disorder (9) and between orbital metabolism and depressive ideation ratings in primary depression (38).

In addition, cocaine-dependent subjects scanned within the first week of cocaine withdrawal as they experienced both depressive symptoms and cocaine craving had elevated glucose metabolism in the medial orbital cortex and the basal ganglia relative to healthy controls (64). The direction of the metabolic abnormality in the orbital cortex resembled that seen in primary depression (Table 1), but the direction of the abnormality in the basal ganglia was opposite that found in the basal ganglia of primary unipolar depressives (37, 22, 35, 53).

Primary and secondary depression thus appear to involve the same general structures, though the patterns and the direction of the abnormalities within these structures in some cases differs between primary and secondary depres-
sive syndromes. This observation provides further support for a circuitry model in which mood disorders are associated with dysfunctional interactions between multiple structures, rather than increased or decreased activity within a single structure (1).

Other neuropsychiatric syndromes that occur comorbidly with MDD may also involve the same neural circuits. For example, the orbital-striatal-pallidal-thalamic circuits have also been implicated in the pathophysiology of obsessive-compulsive disorder (3, 9, 32), potentially providing insight into the comorbidity between depressive and obsessional syndromes (1). The differences found in the ventral PFC between primary and secondary depression parallel the findings in primary and secondary obsessive-compulsive syndromes, in which ventral PFC metabolism is increased in the former but decreased or unchanged in the latter (Table 3).

FUNCTIONAL CORRELATES OF NEUROIMAGING ABNORMALITIES IN DEPRESSION

Regional BF and metabolic abnormalities in depressed subjects may reflect (a) the pathophysiological changes that predispose individuals to recurrent, abnormal mood episodes; (b) the physiological concomitants of signs and symptoms of depression; (c) the physiological correlates of neurotransmitter system dysfunction; (d) the compensatory mechanisms invoked to modulate or inhibit pathological processes; or (e) the areas that have been deactivated during ongoing emotional processing. Hypotheses regarding the functional significance of BF and metabolic correlates of depression thus depend on converging information from functional imaging studies performed in healthy controls or in patients who have related diseases and from electrophysiological and lesion analysis studies of humans and monkeys.

The Dorsal Prefrontal Cortex and Neuropsychological Impairment

The areas of reduced BF and metabolism found in the dorsolateral and the dorsomedial PFC in depression have been linked to the neuropsychological manifestations of depression (2, 65, 66). Regional BF does not increase in these regions during experimentally induced emotional states (2, 12). Instead, in the vicinity of the dorsolateral prefrontal areas where BF and metabolism are decreased in depression, blood flow increases in healthy subjects imaged as they perform tasks involving visuospatial memory, pictorial memory for visual objects, maze navigation, or manipulation of memorized verbal information (2). Dolan et al (65) proposed that this abnormality reflects nonspecific slowing of cognitive processing, based upon their findings that BF is also decreased in
this area in subjects who have schizophrenia, and that the BF reduction correlates with ratings of impoverished speech both in depressed and in schizophrenic subjects. In contrast, Dolan et al (66) more specifically linked abnormal BF in the dorsomedial PFC (which includes the dorsal anterior cingulate gyrus) to impaired performance on neuropsychological testing.

The Orbital Cortex: Potential Role in Correcting Perseverative, Unreinforced Behavior

The abnormal elevations of BF and metabolism in the ventrolateral and orbital areas of the PFC and the pregenual anterior cingulate cortex in depression are thought to reflect physiological activity related to ongoing emotional processing and/or obsessive ruminations (2, 9, 37, 12, 32, 69). Regional BF increases in these areas during experimentally induced sadness or anxiety in healthy subjects and during induced anxiety and/or obsessional states in subjects who have obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, and simple animal phobia (e.g. 2, 8, 9, 10, 68). Lesion analyses in humans and experimental animals; single-unit recording studies in monkeys; and autoradiographic studies in experimental animals exposed to stressors, threats, or appetitive stimuli also support a role for these areas in emotional behavior (12, 50, 67). Finally, these prefrontal areas share the most extensive anatomical connections with subcortical areas implicated in emotional behavior, such as the amygdala, the ventral striatum, and the lateral hypothalamus. Consistent with their proposed role in ongoing emotional processing during depressive episodes, BF and metabolism decrease in the ventrolateral PFC and the orbital cortex as depressive symptoms remit during treatment (Table 2).

Parts of the orbital cortex may be activated in depression to mediate attempts to modulate or inhibit emotional responses (69). Although flow and metabolism are abnormally elevated in the lateral and posterior orbital cortices during depression, the magnitude of the physiological activity in these regions correlates inversely with ratings of depression severity and negative thought frequency (37, 38). Similarly, in obsessive-compulsive or animal phobic subjects scanned during exposure to phobic stimuli and in healthy subjects imaged during induced sadness, BF in the posteromedial orbital cortex increases, yet the magnitude of the BF change correlates inversely with ratings of obsessive thinking, anxiety, and sadness, respectively (9, 10, 68). These findings are consistent with evidence from electrophysiological studies and lesion analyses indicating that the orbital cortex plays a role in correcting behavioral or emotional responses that become inappropriate as reinforcement contingencies change, and in inhibiting emotion-like responses elicited by electrical stimulation of the amygdala (70–72). Thus, in primary major depression, activation of
the posterior orbital cortex may reflect endogenous attempts to break perseverative patterns of negative thought and emotion. In contrast, in some secondary depressive syndromes, a perseverative emotional state may result from disruption of orbital cortex function either by lesions within the PFC or by lesions of the basal ganglia that interrupt neural interactions between the orbital cortex and the striatum (1, 69).

The Amygdala and Emotional Behavior

The amygdala is the only structure in which regional BF and glucose metabolism consistently correlate positively with depression severity (37, 38, 52). The preliminary observation that amygdala metabolism remains abnormally elevated during sleep implies that amygdala hypermetabolism reflects a pathological process rather than a physiological correlate of conscious behaviors or thoughts during scanning (42). In addition to being elevated in the depressed state, BF and metabolism in the left amygdala appear abnormally elevated (though to a lesser extent) in asymptomatic (i.e. between depressive episodes), familial depressives who are not receiving treatment (37). Conversely, during antidepressant drug treatment that both ameliorates the depressive symptoms and helps prevent relapse, amygdala metabolism decreases toward normal (48).

Consistent with these observations, antidepressant drug–treated, remitted subjects with MDD who relapse when given a tryptophan-free diet (which putatively depletes CNS serotonin levels) have higher baseline amygdala metabolism (prior to depletion) than similar subjects who did not relapse (73). These data are thus compatible with the hypothesis that abnormally elevated amygdala activity may confer susceptibility to relapse and recurrence of depressive episodes (1, 74). Finally, abnormal resting metabolism in the amygdala has not been reported in other conditions, suggesting that this finding may be specific to primary mood disorders.

The amygdala has been implicated by single-unit and lesion studies in assigning emotional significance to experiential stimuli and in organizing the behavioral, autonomic, and neuroendocrine manifestations of emotional expression (12, 51). For example, amygdala activity stimulates corticotropin releasing factor (CRF) containing neurons in the paraventricular nucleus of the hypothalamus to release CRF via both direct and indirect projections (75). During depressive episodes, amygdala metabolism correlates positively with plasma cortisol levels (52). Because amygdala hypermetabolism and cortisol release may be linked in depression, the failure to normalize glucocorticoid function during antidepressant treatment may be associated with an increased risk of depressive relapse (76).
CONCLUDING REMARKS

The future of functional neuroimaging research appears bright, as advances in PET and functional MRI (fMRI) technologies and the availability of new radioligands for receptor imaging progressively increase the sophistication of the experimental questions that can be addressed using imaging techniques. In depression research, PET and SPET will be used increasingly to quantify neurotransmitter function, permitting fuller characterization of the neurochemical abnormalities suggested by studies of body fluids, postmortem tissue, and neuroendocrine function. In addition, PET and fMRI will be used to assess hemodynamic changes during the performance of neuropsychological and emotional tasks to examine the functional responses of specific brain structures in depression. The integration of such data with those obtained using lesion analysis and postmortem histopathological approaches will increasingly refine our understanding of the anatomical correlates of melancholia.


Literature Cited


23. Deleted in proof.


38. Drevets WC, Spitznagel E, Raichle ME.
Figure 1a  (legend opposite)

Figure 1b  (legend opposite)
Figure 1c

Areas of abnormally increased blood flow (BF) in subjects with familial, major depressive disorder. The image sections shown are from an image of t-values, produced by a voxel-by-voxel computation of the unpaired t-statistic to compare regional BF between a depressed sample selected according to criteria for familial pure depressive disease (n = 13) and a healthy control sample (n = 33) (37). The positive t-values shown correspond to areas in which BF is increased in the depressives relative to the controls. The PET images from which the t-image was generated have been stereotaxically transformed to the coordinate system of Talairach & Tournoux (11), from which the corresponding atlas outline is shown. Anterior is to the left. Figures 1a and 1c have been modified from Reference 12. Figure 1c is reproduced with permission from Reference 13. This image was generated post hoc to provide optimal localization of the regional BF abnormalities identified using other techniques (37). The abnormal activity in these regions has also been confirmed using regional glucose metabolism images from an independent subject sample (38). (a) Sagittal section at 17 mm to the left of the midline, illustrating areas of increased BF in the amygdala and the medial (MED) orbital cortex of the depressives. (b) The area of increased flow in the left orbital cortex extends laterally to involve areas of the lateral orbital and the ventrolateral (VLPFC) portions of the PFC (37). The x-coordinates locate the sagittal image sections in millimeters to the left of the midline. (c) Coronal t-image section 19 mm caudal to the anterior commissure (i.e., y = -19) showing the area corresponding to increased BF in the left medial thalamus of the depressed subjects relative to the controls. Although specific thalamic nuclei cannot be resolved in PET images, this area of the medial thalamus corresponds approximately to the area of the medial dorsal nucleus that shares extensive, anatomical connections with the amygdala and the ventral prefrontal cortical structures shown in Figures 1a, 1b, and 2 (12).
Figure 2  Coronal (y = 31 mm) and sagittal (x = -3 mm) sections showing negative voxel t-values where glucose metabolism is decreased in depressives relative to controls. This image compares a combined group of familial bipolar and unipolar depressives (n = 17) against controls (n = 12) to localize an abnormality in the subgenual portion of the anterior cingulate gyrus (subgenual PFC) that previously had been identified in an independent subject set (14). The area of reduced metabolism and BF in the subgenual PFC is at least partly accounted for by a corresponding reduction in gray matter volume in the left subgenual PFC, as MRI-based morphometric measures in the same subjects showed that the left subgenual PFC gray matter was reduced in both the bipolar-disordered and the unipolar-depressed groups relative to the control group (14). Reproduced with permission from Reference 14.